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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/773,792

02/06/2004

Thomas W. Dubensky JR.

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MORRISON & FOERSTER LLP
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EXAMINER

GRASER, JENNIFER E

ART UNIT

PAPER NUMBER

1645

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/31/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/773,792

Applicant(s)

DUBENSKY ET AL.

Examiner

Jennifer E. Graser

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213. -

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) 1-21 and 42-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 22-41 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date See Continuation Sheet.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date
:11/7/06,11/2/06,2/9/05,4/10/06,4/21/05,1/6/05, 7/26/04.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II (claims 22-41; species: a mutation in *actA* and *inlB*) in the reply filed on 11/2/06 is acknowledged.

Claims 1-21 and 42-60 are withdrawn as being drawn to a non-elected invention.

Claims 22-41 are currently under examination.

Specification

2. The disclosure is objected to because of the following informalities: The 'Brief Description of Drawings' should be amended to properly correspond to the Figures, e.g., 'Figure 1' should be changed to 'Figures 1A-1C'; 'Figure 2' should be changed to 'Figure 2A-2C', etc., to avoid a printer error at the time of issue.

Appropriate correction is required.

Claim Objections

3. Claim 23 is objected to because of the following informalities: it contains non-elected subject matter which should be removed from the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 22-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite because it attempts to claim the bacterium by function alone. It is unclear what structure is encompassed by 'attenuation both for entry into non-phagocytic cells and for cell-to-cell spread'. The metes and bounds of the claim cannot be understood. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The claim should provide any structural properties which would allow for one to identify the bacterium without ambiguity

Claim 25 is vague and indefinite because it is unclear whether the 'attenuation of the proliferation of the bacterium' is distinct from the attenuation for cell-to-cell spread and/or entry into non-phagocytic cells as recited in claim 21 as those characteristics encompass 'proliferation'.

Claim 27 is vague and indefinite because it is unclear what is encompassed by the phrase 'defective with respect to one or more internalins'. How are they defective? What is encompassed by this language?

Claim 29 is vague and indefinite because it does not describe either the location/type of mutation or the consequence of the mutation, e.g., wherein the mutation results in a bacterium which is attenuated for entry into non-phagocytic cells.

Claim 30 is vague and indefinite because it is unclear what is encompassed by the phrase "defective with respect to ActA". Does this mean the ActA gene has been

Art Unit: 1645

deleted, etc.? The metes and bounds of this language cannot be understood. How is the ActA defective?

Claim 31 is vague and confusing because it is unclear what function the mutation causes.

Claim 39 recites the limitation "the antigen" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 22 does not recite 'an antigen'. Clarification and/or correction is requested.

Claim 41 should be amended to recite that the professional antigen-presenting cell has been "isolated".

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 22-38 are provisionally rejected on the ground of nonstatutory

obviousness-type double patenting as being unpatentable over claims 1-122 of

copending Application No. 10/883,599. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass any bacterium which has been attenuated for proliferation by reaction with a nucleic acid targeted compound that reacts with the nucleic acid (see instant claims 25 and 26). The phenotypes 'attenuated for entry into non-phagocytic cells and for cell-to-cell spread' are forms of proliferation and are, therefore, encompassed in the language of the claims from 10/883,599. Co-pending claims 13 and 16 recite that the microbe is a bacterium, more specifically *L.monocytogenes* and co-pending claim 18 encompasses mutations in both the *actA* and *inlB* genes. Co-pending claims 113 and 120 recite the same tumor antigens as the heterologous antigens recited in instant claim 35. Both applications teach the use of these bacterium as vaccines. Accordingly, since the scope of the instant claims is encompassed by the Genus recited in 10/883,599 the scope of the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 39 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-149 of copending Application No. 10/773,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass methods which use any bacterium which has been attenuated for proliferation by reaction with a nucleic acid targeted compound that reacts with the nucleic acid (see instant claims 25 and 26). The phenotypes 'attenuated for entry into

non-phagocytic cells and for cell-to-cell spread' are forms of proliferation and are, therefore, encompassed in the language of the claims from 10/883,599. Co-pending claims 13 and 16 recite that the microbe is a bacterium, more specifically *L.moncytogenes* and co-pending claim 18 encompasses mutations in both the *actA* and *inlB* genes. Co-pending claims 113 and 120 recite the same tumor antigens as the heterologous antigens recited in instant claim 35. Both applications teach the use of these bacterium in methods inducing an immune response to antigen and methods for treating or preventing a disease in a host. Accordingly, since the scope of the instant claims is encompassed by the Genus recited in 10/773,618 the scope of the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 22-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are broadly drawn to an isolated *Listeria* bacterium which is attenuated both for entry into non-phagocytic cells and for cell-to-cell spread (the elected Group mutations in both actA and inlB). The instant specification has taught a double mutant (mutations in both actA and inlB) which has been deposited with the ATCC as accession number PTA-5562. The instant specification has demonstrated that this mutant strain was eliminated very quickly in the liver as compared to other strains tested, even though it was given in the highest dose. The mutant was shown to elicit an immune response in mice. However, the specification has not taught (through challenge experiments) that this bacterium may provide protection (vaccine) or prevent infections caused by *Listeria*. Treatment of *Listeria monocytogenes* infection has been enabled, but not prevention or protection.

The claims are broadly drawn to obtaining attenuated *Listeria* bacteria by mutating variant nucleotide sequences from many different species of *Listeria* yet the specification has only taught mutation of the actA and inlB genes from *L.monocytogenes*. In the present case, the applicant has neither provided any direction or guidance, nor any working examples in the specification as to any potential mutations of actA and inlB genes from other species of *Listeria* that would satisfy the limitations of the claims. The claims read on any mutation to the *L.monocytogenes* inlB and actA genes, and to homologs thereof, that have the effect of decreasing the activity of the gene product. Just as the breadth of the claims is great, so is the number of potential mutations that may be made. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in

the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue experimentation.

While those participating in the art of the relevant technology (genetic and protein manipulation) are generally highly skilled, the art is also rife with complexity. See also, discussion above in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, *supra*. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are.

The instant claims encompass mutations in control sequences, the coding sequence or in a gene that controls expression of *inlB* or *actA*. It is disclosed that the

function of the mutated gene may be from 25-100% less than the protein produced from a non-mutated gene sequence. See page 28. The specification fails to teach which portions of the actA and inlB gene are necessary for entry into non-phagocytic cells or for cell-to-cell spread. Accordingly, the scope of the instant claims is not enabled.

Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of inlB and actA to target for modifications, in order to produce an attenuated bacterium with the desired phenotype. Applicant's demonstration in the instant Specification that a species of mutant cells may serve as an effective vaccine does not enable one skilled in the art to make mutations in any *Listeria* bacterium, in such a way as to not only attenuate the bacterium through the specific mutation of the inlB and actA, but to also decrease the biological activity in such a way that it is responsible for the resultant attenuated bacterial phenotype. *Genentech Inc. v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling

disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Bowie et al was also cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112-Written Description

11. Claims 22-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an attenuated *Listeria* bacterium which is obtained mutating *any* actA and inlB gene from *any* bacterium of the *Listeria* Genus (elected Group). The claims also are drawn to vaccines comprising these attenuated bacterium. These claims read on mutations of the inlB and actA genes, or attenuated bacteria comprising such polynucleotides, and species homologs thereof. However, the

specification does not provide adequate written description to support either species homologs to *L.monocytogenes* actA and inlB genes, or any mutation resulting in attenuation for entry into non-phagocytic cells and cell-to-cell spread.

There is inadequate written description to support claims to species homologs.

The claims are broadly drawn to obtaining attenuated *Listeria* bacteria by mutating genes from many different species of *Listeria*, yet the specification has only disclose mutations in the inlB and actA genes of *Listeria monocytogenes*.

The applicant has not identified any common structural core which one skilled in the art could use to identify any genus of polynucleotides to be mutated. In essence, the applicant is claiming such mutants comprising homologues only by their functionality, that of attenuated cell-to-cell spread and entry into non-phagocytic cells. More than a statement of biological function is required to satisfy the 112 1st paragraph written description requirement for a genus of DNA molecules. See e.g. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and *Fiers v. Revel*, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In *Amgen v. Chugai*, the Court of Appeals for the Federal Circuit stated that "[i]t is not sufficient to define [a DNA] solely by its principal biological property, e.g. encoding of human erythropoietin." *Id.*, at 1021. Rather, "what is necessary is that [the applicant] provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." *Id.*, at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 ¶1 written description requirement.

More recently, the Federal Circuit again took this position. In the case *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function "is only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus [of claimed cDNAs] that distinguish them from others." *Id.* Thus, it is clear that identification of mutant bacterium by naming the phenotype of the gene it encodes is not sufficient. In the present case, the only description that the applicant has provided for species homologues of *inlB* and *actA* is that they must also be responsible for cell-to-cell spread and entry into non-phagocytic cells. Such a description is clearly insufficient to support the claimed genus. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the *inlB* and *actA* coding regions to target for modifications, in order to produce an attenuated bacterium. While it may be obvious to those in the art to make mutations in a gene or protein, to achieve an attenuated bacterium, once the molecule has been identified as necessary for the virulence of the bacterium, it is not immediately obvious to those in the art as to what mutations will be effective. See e.g., Bowie et al., *Science* 247:1306-1310, page 1306. Bowie et al. presents a discussion on the tolerance of proteins to substitutions in the residue sequence. Although the reference is a discussion of protein substitutions, as the present case is concerned with polynucleotides encoding such proteins, the teachings of the reference are equally applicable to the mutations of the claimed inventions. The reference states first that proteins generally accept a wide variety of

substitutions in their residue sequence. However, it also states that some residues may not be substituted at all without loss of the proteins function. The reference also states that the effects of such substitutions are, currently, highly unpredictable. Thus, one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutation (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity.

As stated above, the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description and enablement requirements. In the present case, not only does the application claim additional undisclosed polynucleotides without such support, it further claims modifications to both the disclosed and undisclosed polynucleotides by the effect of such modifications.

Applicants are claiming bacteria and they are claiming said bacteria comprising a mutation in a nucleotide sequence with a specific structure: function relationship in the claims. "The Applicant's are not claiming polynucleotide sequences per se."

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the coding sequence of the *inlB* and *actA* polynucleotide sequences recited in the claims, but the polynucleotide sequence must additionally be mutated in such a way as to decrease the biological activity (cell-to-cell spread and entry into non-phagocytic cells) in order to attenuate the bacteria. The polynucleotide sequence, as well as the specific mutation(s) of the polynucleotide sequence to accomplish

decreased biological activity of the encoded polypeptide, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

Applicant asserts "there is clearly written descriptive support in the specification for gene sequences that possess 70% or greater identity to the claimed sequences" and cites the specification at page 20, lines 28 through page 21, line 27.

The Specification does not provide any examples or provide any detailed description of the *inlB* and *actA* gene such that one skilled in the art would be aware of, or recognize that Applicant was in possession of, any such mutated bacterium. Applicant has not provided any guidance as to which parts of the gene are susceptible to mutation such that they would result in the expression of an inactive or less active protein thereby resulting in decreased virulence and attenuation of the bacterium. There is no description of any of the gene mutations, or any targets for mutation, that could yield the intended results. Thus, the applicant has not provided any working examples of or any guidance towards, the claimed mutations. The applicant is therefore claiming, as indicated in the prior action, a genus of mutated bacteria solely by their intended effects, without providing any structural or other information by which one skilled in the art could identify the claimed inventions.

The application need not describe every possible change to the coding sequence for a polypeptide that would result in meeting the claims' functional limitations. However, such does not absolve the Applicant of the need to provide some structural description by which those in the art could distinguish mutated genes resulting in the attenuated bacterium. Applicant must describe a representative number of species for a claimed

genus, but what is now claimed, is a highly variable genus (mutant poly-nucleotides) which result in variable levels of biological activity, and expression (see all claims), for which deposited mutant strain is not representative.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 22-24, 27-30, 32, 37, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Appelberg et al (Infect. Immun. Feb. 2000. 68(2): 912-914).

Appelberg et al teach mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread. They teach an isolated *Listeria monocytogenes* mutants which are defective in the ***actA*** gene, the *plcB* gene and the *inlA* and ***inlB*** genes. These mutant strains were shown to be less virulent than wild-type strains. See abstract. These mutants were injected into mice and the immune response was monitored. The term “vaccine” is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A “physiologically acceptable carrier” reads on water and therefore would be inherent in the preparation of the mutants. The reference specifically recites

that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways". See paragraph bridging pages 913-914.

14. Claims 22-24, 27-30, 32, 37, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Drevets (Infect.Immun. Jan. 1998. 66(1): 232-238).

Drevets teaches mutants of *Listeria monocytogenes* which are defective in cell invasion and cell-to-cell spread. Drevets teaches isolated *Listeria monocytogenes* mutants with deletions of the *actA*, *inlA*, *inlB*, *inlAB*, *plcA* and *plcB*. These mutant strains were shown to be less virulent than wild-type strains. See abstract. These mutants were injected into mice and the immune response was monitored. The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the mutants.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Appelberg et al (Infect. Immun. Feb. 2000. 68(2): 912-914), as applied to claims 22-24, 27-30, 32, 37, 38, 39 above.

The teachings of Appelberg et al are set forth above. The reference teaches mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread. They teach an isolated *Listeria monocytogenes* mutant which is defective in the **actA** gene, the *plcB* gene and the *inlA* and ***inlB*** genes. These mutant strains were shown to be less virulent than wild-type strains. See abstract. Although the reference does not specifically teach a mutant with mutations in both the ActA and internalin pathways, it would have been prima facie obvious to one of ordinary skill in the art to generate such a mutant because Appelberg et al specifically recite that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways" because they hypothesize that invasion of hepatocytes by an ActA mutant is mediated by the InlAB-induced internalization of the bacteria directly by the hepatocytes". It is disclosed that this is critical to the way in which the bacterium can cause severe infection. See paragraph bridging pages 913-914. Accordingly, one of ordinary skill in the art would have been motivated to produce a mutant deficient in both ActA and inlB in order to find a way of treating such a virulent infection.

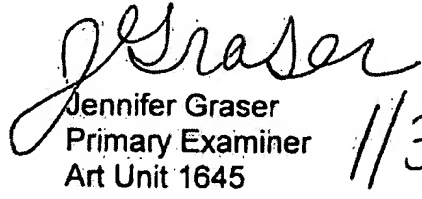
17. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.


Jennifer Graser
Primary Examiner
Art Unit 1645
1/31/07